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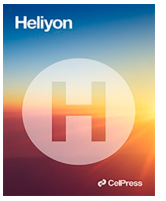

Review article

Burden of active tuberculosis among patients with diabetes mellitus in Sub-Saharan Africa: A systematic review and meta-analysis

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ABSTRACT

Background: The simultaneous occurrence of diabetes mellitus and tuberculosis presents a significant health challenge, complicating diagnosis, treatment, and outcomes. Despite this, tuberculosis screening is not routinely conducted for diabetes patients, and limited information exists regarding tuberculosis prevalence among diabetics in Africa. Thus, this study aimed to determine the pooled prevalence of tuberculosis among diabetes mellitus patients in Sub-Saharan Africa.

Methods: A systematic search was conducted in PubMed, Medline, Google Scholar, and African Journal online library databases to identify studies reporting tuberculosis burden among diabetes patients in Sub-Saharan Africa. Data extraction was performed using an Excel spreadsheet, with analysis carried out in Stata version 14. The pooled prevalence was estimated using a DerSimonian-Laird random-effects model. Heterogeneity among studies was assessed using I-squared test statistics, and subgroup analyses were conducted to identify heterogeneity sources. Risk of bias assessment and sensitivity analysis were also performed.

Results: The systematic review and meta-analysis included twelve studies with 13,002 participants. The combined prevalence of tuberculosis among diabetes patients in Sub-Saharan Africa was 4.11 % (95 % confidence interval: 2.97–5.25); I2 = 89.4 %). Subgroup analysis revealed a pooled tuberculosis prevalence of 4.6 % among diabetes patients in East Africa and 2.36 % in Southwestern African countries.

Conclusions: This research indicates an elevated prevalence of tuberculosis among diabetes patients in sub-Saharan Africa. The findings highlight the urgent need for tuberculosis screening in diabetes patients and the implementation of effective prevention strategies to address the dual burden of comorbid tuberculosis and diabetes mellitus.

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1. Introduction

Tuberculosis (TB) is a contagious disease caused by *Mycobacterium tuberculosis* that primarily affects the lungs [1]. According to the World Health Organization (WHO) global tuberculosis report, an estimated 10·6 million people had TB in 2021, one-fourth of whom are from Africa (2.5 million people). In the same year, 1.7 million people died from TB globally, with 417,000 deaths in Africa (more than 25 %) [2]. TB has an estimated incidence rate of 201 per 100,000 populations, with the highest burden in Sub-Saharan Africa (SSA). Additionally, the African continent exhibits a 3.6 % prevalence rate of TB that is resistant to drugs [3]. Human Immunodeficiency Virus (HIV) infection affects an estimated 25.7 million people living in Africa, with southern Africa having the highest prevalence. One study found that metabolic syndrome was more prevalent among patients with TB in SSA than in the general population [4].

On the other hand, DM is a metabolic disorder characterized by high blood sugar levels, affecting over 537 million people worldwide. Without sufficient efforts to address this growing burden, it is predicted that the number of people with DM will reach 578 million (10.2 %) by 2030 and escalate to 700 million (10.9 %) by 2045 [5,6]. In, type 2 DM is more prevalent, accounting for more than 90 % of diabetes cases, with an estimated prevalence of 7.5 % in Africa and the highest prevalence in countries such as South Africa and Swaziland [7,8].

The coexistence of TB and DM presents a major public health challenge as these two diseases have a synergistic effect, with one increasing the risk of developing the disease. It increases the risk of TB twofold to threefold, death during TB treatment twofold, relapse after TB treatment is complete, and multidrug-resistant TB twofold [9,10]. In 2020, diabetes mellitus is estimated to contribute to 370, 000 new cases of tuberculosis [11]. The global prevalence of diabetes among people with TB was estimated to be 15 % in 2019, with a prevalence of 9.3 % in the general adult population [12]. Millions of people require coordinated care and follow-up to optimize both diabetes and TB management, approximately 1.5 million people need coordinated care and follow-up [13,14]. In SSA systematic reviews, the prevalence of TB in DM ranges from 0.38 to 14 % [15]. Several studies have demonstrated that factors such as a weakened immune system, poor glucose control, lung damage, malnutrition, poor living conditions, age, and limited access to healthcare are risk factors for TB [15–18].

The increasing incidence of DM in low-income and middle-income countries poses a significant threat to the control of TB and could hinder efforts to achieve the Sustainable Development Goal of ending TB by 2030. However, owing to the presence of other diseases, as well as potential drug interactions and adverse effects, the diagnosis and treatment of these two diseases can be complicated [19,20].

To effectively diagnose, prevent, and manage this double burden, it is crucial to understand the impact of TB in individuals with DM [9]. Despite this, there is limited information about the prevalence of TB in patients with DM, which makes it difficult to manage and control both the diseases. Furthermore, there is a lack of comprehensive reviews and statistical analyses on the occurrence of tuberculosis in diabetic patients, especially within Sub-Saharan Africa (SSA). This research sought to conduct a comprehensive assessment of the latest information concerning the frequency of TB among individuals with diabetes, as well as the consequences of these intersecting health crises in SSA.

2. Methods

A systematic review and meta-analysis were undertaken to determine the combined prevalence of tuberculosis in diabetes patients within Sub-Saharan Africa (SSA). The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21] (Supplementary file 1).

2.1. Searching strategy

Extensive literature searches were performed across various databases, including MEDLINE, PubMed, Google Scholar, EMBASE, African Journal Online Library, and online university research repositories. The search focused on identifying studies related to tuberculosis prevalence among diabetic patients in SSA. Search terms included "magnitude," "prevalence," "proportion," "burden," "incidence," "tuberculosis," "TB," "diabetes patients," "DM," and "SSA." Gray literature from online library repositories and manual reference checks were also incorporated. The search encompassed all publications up to July 2023.

2.2. Eligibility criteria

The review included all observational studies conducted in SSA countries on patients with any type of diabetes registered in DM clinics for care. These studies reported the incidence or prevalence of either pulmonary or extra-pulmonary tuberculosis and were published in English from the inception of relevant databases. Studies that did not provide information on the primary outcome of interest, were not objectively designed to assess it, or were published as reviews, meta-analyses, or case series were excluded from the analysis.

2.3. Outcome measurements

The primary outcome of this systematic review and meta-analysis was the presence of TB among diabetes patients. A positive TB status was diagnosed when a patient met at least two of the following criteria: positive sputum smear by microscopic examination of

Ziehl-Neelsen-stained sputum slides for acid-fast bacilli, chest radiographs with suggestive features of TB, and/or clinical symptoms and signs of TB [22]. The prevalence and standard error of prevalence were calculated using the metan-prevalence standard error command.

2.4. Quality assessments and data extraction

Two independent authors evaluated the quality of the included studies using a checklist developed by the Joanna Briggs Institute (JBI) as a quality appraisal tool for observational studies [23]. Data extraction was performed by two extractors (GAK and YSA) using standardized extraction checklists in Microsoft Excel. Endnote version X7.2 was used to combine search results from databases and remove duplicate articles. Studies were screened and excluded based on titles and abstracts. The remaining articles' full texts were assessed for eligibility according to predetermined inclusion and exclusion criteria. Extracted data included authors' names, publication years, research locations, regions, sample sizes, tuberculosis prevalence, and quality ratings. Disagreements were resolved through discussions among the reviewers. If an independent reviewer could not reach an agreement, a third reviewer (GAA) was consulted to resolve the conflict. Studies with a final quality rating checklist score ≥50 % were included (Supplementary File 2).

2.5. Data synthesis and statistical analysis

After extracting the data, it was moved from Microsoft Excel to STATA 14.1 for analysis. Heterogeneity among studies was assessed using the inverse variance (I2) test. I-squared values were categorized as moderate (30–60 %), substantial (60–90 %), or considerable (90–100 %). Given the significant heterogeneity (I2 >89.4 %, P-value <0.001), the Freeman–Tukey double arcsine transformation method with the Der-Simonian and Laird random-effects model [24] was used to determine the pooled prevalence of TB in diabetic patients. Egger's and Begg's tests were employed to check for publication bias. A leave-one-out sensitivity analysis was performed to evaluate the influence of small studies on the TB prevalence among diabetic patients.

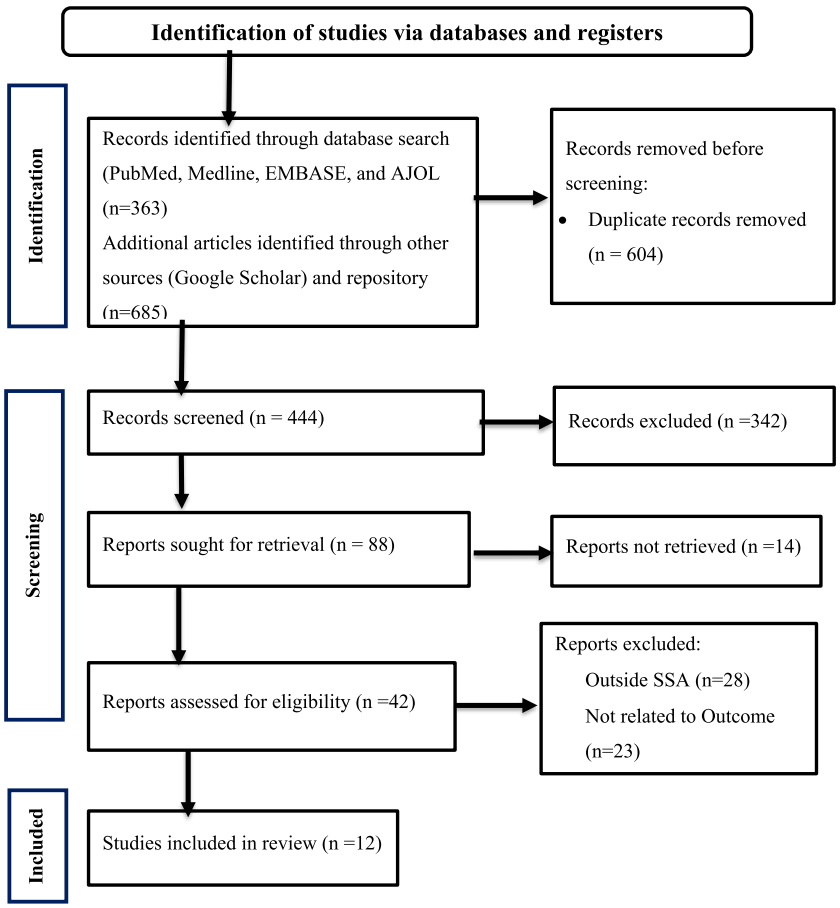

Fig. 1. PRISMA 2020 flow diagram of articles screened and the selection process on prevalence of tuberculosis among diabetes patient in SSA.

3. Results

3.1. Study selection

The initial search yielded 1048 articles on TB prevalence in DM patients. After removing 604 duplicates, 444 articles remained. Title and abstract screening eliminated 342 irrelevant articles, leaving 102 studies for further review. Sixty more were excluded as irrelevant, resulting in 42 full-text articles for eligibility assessment. Thirty articles were then excluded due to various reasons, including studies conducted outside SSA, insufficient data, non-diabetic study populations, and lack of outcome interest. Ultimately, 12 studies were included in the meta-analysis (Fig. 1).

3.2. Characteristics of included studies

In the current meta-analysis, 12 observational studies (13,002 diabetes patients) were included to estimate the pooled prevalence of TB among patients [16–18,25–33]. The studies included in the analysis were published from 1999 to 2022. Regarding study design, the majority 12 (85.7 %) were cross-sectional studies. The sample size of the studies ranged from 207 to 5870. The lowest prevalence (1.76 %) of DM was reported in a study conducted in Ethiopia [25], whereas the highest prevalence (6 %) was reported in a study conducted in three west African countries [32]. Seven SSA countries were included in this meta-analysis. Six studies were from Ethiopia [16,18,25–27,31], two from Tanzania [29,30], two from South Africa [17,33], one from West African countries (Benin, Senegal, and Guinea) [32], and one from Kenya [28] (Table 1).

3.3. Pooled prevalence of tuberculosis among diabetes patients

The pooled prevalence of TB among diabetes patients with DM was reported to be 4.11 % (95 % CI: 2.97, 5.25 %). Significant heterogeneity was observed across the studies (I2 = 89.4 %, p value < 0.001) (Fig. 2). Among individual studies, the highest prevalence of TB (6 %) and the highest rate of 9.86 per 100 years of observation were reported in studies conducted in Ethiopia.

3.4. Subgroup analysis

Significant heterogeneity was noted among the studies (I2 = 89.4 %, p < 0.001), prompting a subgroup analysis based on study location, mean age, research design, and publication year. The age-based subgroup analysis revealed that the combined TB prevalence was 4.18 % (95 % CI = 2.90, 5.48) for individuals 45 years and older, and 3.99 % (95 % CI = 1.66, 6.31) for those under 45. In African regions, the aggregated TB prevalence among DM patients was 4.6 % (95 % CI = 3.38, 5.82) in East Africa and 2.36 % (95 % CI = 1.48, 3.23) in Southwest Africa. Regarding study methodology, the pooled TB prevalence in DM patients was 3.96 % (95 % CI = 2.7, 5.26) for cross-sectional studies and 4.1 % (95 % CI = 2.7, 5.25) for retrospective cohort studies. A decrease in TB burden was observed, from 4.79 % (3.96, 5.62) in studies published before 2019 to 2.7 % (1.48, 3.92) after 2019 (Table 2).

3.5. Publication bias

The funnel plots' graphic asymmetry indicated publication bias (Fig. 3). This was further confirmed by significant p-values (p < 0.001) in both Begg's and Egger's tests. The trim-and-fill method was employed to assess publication bias. Despite the potential absence of five studies, the results remained largely unchanged after the addition of five virtual studies, suggesting the stability of this meta-analysis's findings (Fig. 4).

Table 1
Description of studies included in the meta-analysis of TB among DM patient in SSA.

No	Authors (Publication year)	Country	Region	Study design	Sample size	TB infected	Prevalence	Quality rating
1	Abera et al., 2018(25)	Ethiopia	East Africa	CS	207	11	5.31	6
2	Amare et al., 2013(16)	Ethiopia	East Africa	CS	255	14	5.49	7
3	Andualem et al., 2021(26)	Ethiopia	East Africa	CS	258	7	2.71	6
4	Berkowitz et al., 2018(17)	South Africa	South Africa	CS	440	13	2.95	7
5	Feleke et al., 1999(27)	Ethiopia	East Africa	CS	1352	78	5.77	7
6	Gedefaw et al., 2020(18)	Ethiopia	East Africa	RC	433	26	6.0	7
7	Kirui et al., 2012 [28]	Kenya	East Africa	CS	1376	77	5.59	6
8	Makuka et al., 2022(29)	Tanzania	East Africa	CS	623	11	1.76	6
9	Swai et al., 1990(30)	Tanzania	East Africa	CS	1250	70	5.60	6
10	Tiroro et al., 2015 [31]	Ethiopia	East Africa	RC	681	26	3.82	7
11	Wachinou et al., 2021(32)	West Africa	west Africa	CS	5870	114	1.94	7
12	Webb et al., 2009(33)	South Africa	South Africa	CS	258	9	3.49	7

Abbreviations: CS, cross-sectional study; RCS, retrospective cohort study; TB, tuberculosis.

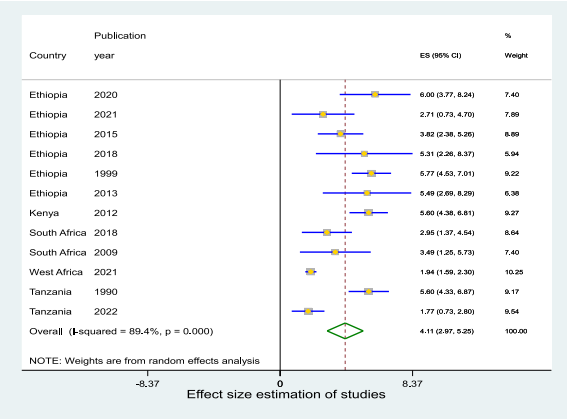

Fig. 2. The forest plot showcases the aggregated TB prevalence among DM patients in Sub-Saharan Africa. A diamond shape represents the overall effect size of 4.11 %, with its width indicating the 95 % confidence interval (2.971–5.25). The plot's vertical axis displays each study's standard error, while the horizontal axis shows individual study effect sizes. A vertical line denotes no effect. Each study's effect size is depicted by a box, with a line intersecting it to show the study's confidence interval.
Abbreviations: ES, effect size; CI, confidence interval.

Table 2
Subgroup analysis on prevalence of tuberculosis among diabetes mellitus patient in SSA.

Subgroups	Category	Number of studies	Effect size (95 % CI)	I-Square	p-value
Region	East Africa	9	4.6 (3.38, 5.82)	81.4 %	0.0001
	Southwest Africa	3	2.36(1.48, 3.23)	37.1 %	0.204
Years of publication	<2019	8	4.79 (3.96, 5.62)	50.2 %	0.05
	≥2019	4	2.7(1.48, 3.92)	77.0 %	0.004
Study design	CS	10	3.96(2.7, 5.26)	90.3 %	0.0001
	RCS	2	4.1 (2.7, 5.25)	6.5 %	0.107
Average age	<45 years	4	3.99 (1.66, 6.31)	80.6 %	0.0001
	≥45 years	6	4.18 (2.90, 5.48)	92.6 %	0.0001

Abbreviations: CS, Cross-sectional study; RCS, Retrospective Cohort Study; CI, Confidence Interval.

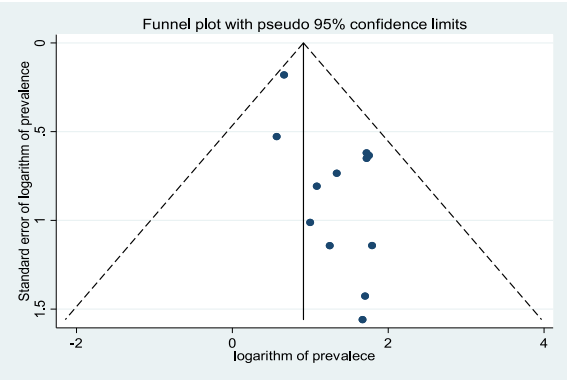

Fig. 3. This funnel plot examines publication bias in studies reporting TB prevalence among DM patients in SSA. The symmetrical distribution of studies suggests an absence of publication bias. The Y-axis shows the standard error of prevalence logarithm, and the X-axis presents the study outcome or effect magnitude. A dotted diagonal line forms the 95 % confidence interval funnel, with a vertical line indicating no effect. Data points represent studies reporting TB incidence in diabetic individuals.

3.6. Sensitivity analysis

Sensitivity analysis was used to assess the effect of a single study on the prevalence of tuberculosis among patients with diabetes by excluding each study individually. The graph below presents a sensitivity analysis forest plot from a meta-analysis, examining the effect of excluding individual studies on the pooled prevalence estimate. Each horizontal line represents the confidence interval for an

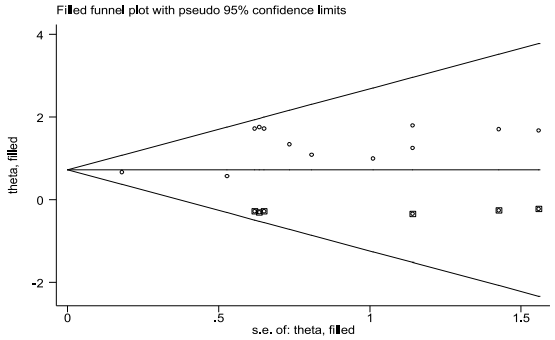

Fig. 4. This funnel plot illustrates a trim-and-fill analysis of publication bias in studies reporting TB prevalence among DM patients in SSA. The vertical axis displays theta (filled), while the horizontal axis shows the effect size's standard error. A dotted diagonal line represents the 95 % confidence interval funnel, and a horizontal line indicates no effect. Small dots denote unreported articles, while larger dots represent missed publications documenting TB cases in diabetic individuals.

individual study when omitted, with circles indicating point estimates. The vertical line marks the overall estimate, and the plot shows that omitting any single study does not significantly shift the point estimates beyond the overall effect, suggesting that the meta-analysis results are stable and not overly influenced by any one study. This robustness is crucial for the reliability of the meta-analysis conclusions regarding the prevalence of TB among diabetes patients in SSA (Fig. 5).

4. Discussion

The concurrent presence of TB and DM poses distinct challenges in patient care. The immune effects of DM on TB infection can complicate treatment outcomes and lead to drug resistance. To effectively diagnose, prevent, and control this double burden, it is critical to estimate the TB burden in patients with DM [12].

This study revealed that the pooled prevalence of TB among patients with diabetes in SSA was found to be (4.11 %). This result aligns with findings from a systematic review and meta-analysis of African Asian nations (4.72 %) [33], an Ethiopian meta-analysis (4.14 %) [34], and another comprehensive review examining the TB-diabetes relationship, which revealed that DM patients face a 3.59 times higher risk of developing active TB [35], and primary studies in Bangladesh (3.4 %) [36]. However, it was higher than that reported in a primary cohort study in Australia (7.4/100,000/year) [37], Sri Lanka (0.1 %) [38], and a primary study in the Republic of Korea (0.59 %) [39]. Various factors could account for this discrepancy, including the quantity of studies, diagnostic methods employed, and the level of disease prevalence. For instance, the prevalence of TB in Sri Lanka is estimated by the WHO to be 0.06 %, and Sri Lanka has reported a prevalence of DM of 7.3 %, which is lower than that in African countries [40]. Overall, this finding implies the need for public health interventions, including screening, improved diabetes management, and integrated care programs, to reduce the prevalence of TB among patients with diabetes.

The study's subgroup analysis revealed significant variations in TB prevalence among diabetic patients across sub-Saharan Africa. Eastern Africa exhibited the highest prevalence (4.6 %), while southwestern African countries showed the lowest pooled prevalence

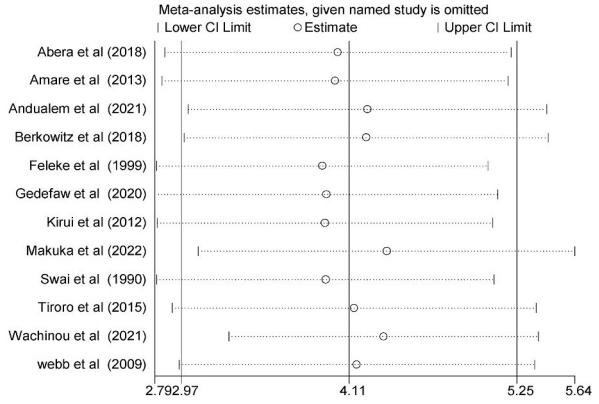

Fig. 5. A sensitivity analysis of the pooled TB prevalence among DM patients in SSA is presented in this forest plot. It demonstrates the stability of the overall effect size estimate from various studies. Horizontal lines show each study's effect size and 95 % confidence interval, with a diamond at the bottom representing the pooled effect size. The size of central points on each line indicates individual study weights.

(2.36 %). This may be due to the high prevalence of diabetes in East African countries, as well as variations in diabetes management, which contributes to the higher TB prevalence rate among diabetes patients. Due to numerous factors, such as lack of access to healthcare, poverty, and limited awareness of diabetes care, diabetes affects a massive portion of the East African population [41]. Thus, it is essential to strengthen the healthcare systems and public health interventions to address the dual burden of TB and diabetes in East Africa.

According to the subgroup analysis by publication year in this systematic review and meta-analysis, studies published before 2019 reported a higher pooled prevalence of TB among diabetic patients (4.79 %) than those published after 2019 (2.7 %). It is possible that improved screening and diagnosis have contributed to a decrease in the prevalence of TB among diabetic patients; better management of diabetes has resulted in better blood sugar control, a stronger immune system, and a reduction in the risk of TB infection and reactivation among diabetic patients. Improved infection control measures have improved access to TB treatment [42]: The decrease in TB trends among diabetes patients, which could be considered a positive development in combating these diseases.

This systematic review and meta-analysis emphasizes the necessity for diabetes and TB programs to work together, stressing the importance of an integrated approach in managing both conditions. It also underscores the need to prioritize preventive strategies, early identification, and effective treatments for diabetic patients. Furthermore, the study accentuates the significance of additional research to elucidate the connection between diabetes and tuberculosis, as well as to create interventions aimed at lessening the impact of both diseases.

4.1. Limitation of the study

Interpreting the results of this study should take into account some limitations. Firstly, the analysis was restricted to primary studies published in English, potentially introducing bias. Secondly, the included studies exhibited heterogeneity, possibly due to unmeasured characteristics. The majority of eligible studies identified through our comprehensive search strategy were conducted in East Africa. Depending on the extent of this impact, the estimates may lack precision or representativeness.

5. Conclusion

To summarize, this research demonstrates that individuals with diabetes exhibit a greater prevalence of TB compared to the general population. This may be due to the weakened immune system caused by diabetes, which makes individuals more susceptible to infections [43]. The findings highlight the need for improved screening and monitoring of TB in patients with diabetes to prevent transmission, development of complications and decrease the risk of TB-DM comorbidity. Furthermore, screening for TB in patients with diabetes and lifestyle interventions may improve early detection. Overall, this study emphasizes the importance of addressing the intersection between diabetes and TB to improve public health outcomes.

CRediT authorship contribution statement

Gizachew Ambaw Kassie: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Getachew Asmare Adella:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Beshada Zerfu Woldegeorgis:** Writing – original draft, Visualization, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Afework Alemu:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Funding acquisition, Data curation. **Amanuel Yosef Gebrekidan:** Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Kirubel Eshetu Haile:** Writing – review & editing, Writing – original draft, Supervision, Software, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Amelework Gonfa Efa:** Writing – original draft, Supervision, Software, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Gedion Asnake Azeze:** Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Investigation, Data curation, Conceptualization. **Yordanos Sisay Asgedom:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data used in the generation of the results presented in this manuscript will be made available upon reasonable request from the corresponding author.

Ethics approval and consent to participate

Not applicable.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40140.

Abbreviations

CI	Confidence Interval
JBI	Joanna Briggs Institute
DM	Diabetes Mellitus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SSA	Sub-Saharan Africa
PTB	Pulmonary Tuberculosis
TB	Tuberculosis
WHO	World Health Organization

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